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**Title:**

# BASELINE PROGESTERONE ELEVATION AT THE ONSET OF OVARIAN STIMULATION IS NEITHER CORRELATED WITH EMBRYO QUALITY NOR EUPLOIDY RATE

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**Objective:**

Elevation of serum progesterone (P) during day 2 or 3 of a menstrual cycle is an uncommon phenomenon during ovarian stimulation cycles. The exact mechanism of this phenomenon is still unknown, although incomplete luteolysis, endogenous production by the adrenals, and ovarian aging have been described as potential causes of baseline progesterone elevation (BPE). Numerous authors have postulated that baseline progesterone elevation predicts decreased implantation in fresh IVF cycles, (Hamdine et al. 2014) however, to date, there is no published evidence clarifying a correlation with morphological appearance and genomic competence. Thus, the influence of elevated P levels at the start of ovarian stimulation on embryonic characteristics requires further investigation. The objective of this study is to analyze the potential association of BPE on ovarian stimulation outcomes, oocyte maturity, embryonic quality and embryonic euploidy in IVF/PGT cycles.

**Design:**

Retrospective cohort analysis from an academic, private IVF center

**Material and Methods:**

The study included infertile couples who underwent IVF with GnRH antagonist stimulation starting on the day 3 of the cycle from 2016-2020. Trophectoderm biopsy and pre-implantation genetic testing for aneuploidy (PGT-A) with NGS were performed on select blastocysts reaching criteria for trophectoderm biopsy (≥4CC Gardner´s). Cohorts were segregated in two groups: Group 1: cycles with the presence of normal P levels (P <1.5 ng/mL) on day 3 of the cycle; Group 2: cycles with BPE on day 3 of the cycle (P ≥1.5 ng/mL). Patients with OCP pretreatment, presence of an active follicle on day 3, ovum donation, balanced translocations and severe male infertility cases were excluded from the analysis. Demographic, COH parameters, blastulation, and euploidy rates were evaluated. Comparative statistical tests and an adjusted mixed model with a GEE framework was utilized for statistical analysis. A sample size of 163 blastocysts per group was calculated to create an 80% power to detect a difference of 15% on euploidy rates ($\alpha$=0.05).

**Results:**

A total of 16892 blastocysts from 3527 cycles with normal P were compared to202 blastocysts from 46 cycles with BPE. A baseline P elevation prevalence of 1.2% was found in all cycles analyzed. Significant differences were found in AMH, baseline estradiol, day of ovulation trigger and estradiol at ovulation trigger between cohorts (Table 1). On an unadjusted analysis, no differences were found in mean number of oocytes retrieved, oocyte maturity rate, fertilization, blastulation, and utilizable blastocyst rate among cohorts. The average of good, moderate and fair morphologic grading blastocysts were comparable among groups. Aneuploidy rates were different between groups (Normal P= 44.26% vs. BPE= 32.93%,p=0.02), however euploidy and inconclusive embryo rates were comparable between cohorts (Table 1). After adjusting for age, BMI, AMH, days of stimulation and number of fertilized oocytes per cycle, no association was found between BPE and blastulation rates (OR=0.98, CI95% 0.56-1.72, p=0.97). Also, there were no associations between high P on day 3 and euploidy rates (OR=1.05, CI95% 0.61-1.80, p=0.84), or aneuploidy rates (OR=0.86, CI95% 0.52/1.44, p=0.58).

**Conclusion:**

Elevated progesterone at the beginning of the menstrual cycle during ART treatment does not appear to compromise the embryonic quality for patients who undergo freeze all/PGT cycles. Our study is the first to demonstrate that BPE is not associated with

impaired number of oocytes retrieved, oocyte maturity rates, embryonic quality or euploidy rates when compared with cycles with normal P on day 3. The clinical significance of BPE and success rates following an embryo transfer has yet to be established. Further research including detailed endocrine monitoring is needed to better understand if BPE represents a normal variation within menstrual cycles or if it embodies a measurable consequence derived from a subtle ovarian dysfunction.


## Support

None.


## Table 1

Demographic, ovarian stimulation parameters and PGT analysis of populations analyzed.

| | Normal baseline progesterone (P <1.5 ng/mL) | | Baseline progesterone elevation (P ≥1.5 ng/mL) | | |
|---|---|---|---|---|---|
| | n= 3527 cycles | | n=46 cycles | | |
| | Mean | SD | Mean | SD | p value |
| **Age (years)** | 37.55 | 4.19 | 37.56 | 4.88 | 0.98 |
| **BMI (kg/m$^2$)** | 24.07 | 4.48 | 24.24 | 4.12 | 0.59 |
| **AMH (ng/ml)** | 2.92 | 3.14 | 1.59 | 1.17 | **0.001** |
| **Day 3 FSH (IU/mL)** | 7.46 | 3.11 | 7.94 | 5.30 | 0.68 |
| **Day 3 Estradiol (pg/mL)** | 44.79 | 20.95 | 59.79 | 48.44 | **0.04** |
| **Day 3 Progesterone (ng/mL)** | 0.45 | 0.21 | 2.22 | 0.84 | **<0.001** |
| **Day of ovulation trigger** | 11.62 | 1.26 | 12.23 | 1.17 | **0.004** |
| **P on the day of ovulation trigger (ng/ml)** | 0.91 | 0.50 | 1.25 | 1.26 | 0.34 |
| **Estradiol on the day of ovulation trigger (pg/mL)** | 2136.50 | 1161.81 | 1813.03 | 1287.87 | **0.03** |
| **Days of gonadotropin administration** | 8.62 | 1.26 | 9.23 | 1.17 | **0.004** |
| **Gonadotropin cumulative dose (IU)** | 3620.52 | 1218.34 | 3971.06 | 1369.86 | 0.22 |
| **Previous IVF cycles** | 0.47 | 0.97 | 0.85 | 1.95 | 0.25 |

| | | | | | |
|---|---|---|---|---|---|
| **Oocytes Retrieved** | 14.45 | 8.85 | 13.98 | 9.32 | 0.53 |
| | **N** | **%** | **N** | **%** | **Xi2** |
| **Oocyte maturation rate** | 36139/47974 | 75.33% | 406/559 | 72.63% | 0.46 |
| **Fertilization rate** | 28750/36139 | 79.55% | 330/406 | 81.28% | 0.69 |
| **Blastulation rate** | 16892/28750 | 58.75% | 202/330 | 61.21% | 0.56 |
| **Utilizable/Biopsied embryos rate** | 13882/16892 | 82.18% | 164/202 | 81.19% | 0.87 |
| **Embryo quality rates:** | | | | | |
| • **Good** | 11117/16892 | 65.81% | 128/202 | 63.37% | 0.67 |
| • **Moderate** | 2887/16892 | 17.09% | 31/202 | 15.35% | 0.55 |
| • **Fair** | 2888/16892 | 17.10% | 43/202 | 21.29% | 0.15 |
| **Euploidy rate** | 7141/13882 | 51.44% | 102/164 | 62.20% | 0.06 |
| **Aneuploidy rate** | 6144/13882 | 44.26% | 54/164 | 32.93% | **0.02** |
| **Inconclusive rate** | 597/13882 | 4.30% | 8/164 | 4.88% | 0.72 |

## References:

1. Hamdine O, et al. Elevated early follicular progesterone levels and in vitro fertilization outcomes: a prospective intervention study and meta-analysis. Fertil Steril. 2014 Aug;102(2):448-454.e1. doi: 10.1016/j.fertnstert.2014.05.002.